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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/631,224	07/28/2003	Cheng J. Cao	DAM 581-02	3741

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US ARMY SOLDIER AND BIOLOGICAL CHEMICAL COMMAND
OFFICE OF THE CHIEF COUNSEL/IP TEAM (BLDG E4435)
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APG, MD 21010-5424

EXAMINER	
SHAHNAN SHAH, KHATOL S	

ART UNIT	PAPER NUMBER
1645	

MAIL DATE	DELIVERY MODE
01/26/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/631,224	CAO ET AL.	
	Examiner	Art Unit	
	Khatol S. Shahnan-Shah	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 September 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15,23 and 24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15, 23 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

RESPONSE TO AMENDMENT

1. The response filed 9/23/2008 has been entered into the record. Claims 1-14 and 16-22 have been previously cancelled. Claims 15, 23 and 24 are pending and are under examination.

Rejections Maintained

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Rejection of claims 15, 23 and 24 under 35 U.S.C. 103 (a) made in paragraph 6 of the office action mailed April 24, 2008 is maintained.

The rejection was as stated below:

Claims 15, 23 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Letertre et al. (Molecular and Cellular Probes, vol.17, pp. 139-147, 2003) in light of O'Connell et al. (23rd Army Science Conference, December 2002), and further in view of Borst et al. (Infection and Immunity vol. 61, no. 12, pp. 5421-5425, 1993 and sequence alignment # STAENAB) and further in view Padmapriya et al. (US 2005/0233345A1 and sequence alignment # AED45640).

Note: It is noted that Real –Time fluorescence PCR works similarly as evidenced by O'Connell et al below:

O'Connell et al. (23rd Army Science Conference, December 2002) teach "Real-time fluorescent PCR" process steps that involve the addition of a third small fragment of DNA to the reaction mixture. The DNA/RNA detection reaction combines standard PCR with a third reagent, a probe DNA molecule that hybridizes to a target sequence

between the sequences bound by the two PCR primers. The probe is labeled at one end with a fluorescent dye molecule and at the other end with a molecule that quenches the fluorescence of the dye molecule, such that the proximity of these two molecules results in a quenching of the dye's fluorescence. When a thermostable DNA polymerase extends one of the two primers into the area where the probe is bound, the 5' nuclease activity of Taq DNA polymerase degrades the probe and releases the fluorescent and quencher molecules bound to the probe ends. The separation of the dye and the quencher results in an increase in the overall fluorescence of the sample mixture. A detector in the PCR instrument continually monitors and records the fluorescence present in the sample. Significant accumulation of fluorescence in the sample above background level indicates a positive detection of the target DNA.

Claim 15 as amended is drawn to a method of determining the presence of staphylococcal enterotoxin A gene in a sample, **comprising:**

contacting a target nucleic acid sequence which **comprises a portion of the *S. aureus ent A* gene encoding staphylococcal enterotoxin A,** with polymerase chain reaction reagents specific for the target nucleic acid sequence, the polymerase chain reaction reagents including a primer selected from the group consisting of a forward primer having a specific sequence selected from the group consisting of SEQ ID NO: 3, SEQ ID NO: 4 and combinations thereof, and a reverse primer **having** a specific sequence selected from the group consisting of SEQ ID NO: 5, SEQ ID NO: 6 and combinations thereof, a polymerase enzyme, and a nucleic acid probe, wherein the nucleic acid probe further **comprises:**

a nucleic acid sequence that hybridizes to a portion of the target nucleic acid sequence **wherein the portion is unique to the nucleic acid encoding staphylococcal enterotoxin A,** and wherein the nucleic acid sequence of the nucleic acid probe is selected from the group consisting of SE-Q ID NQ. I, SEQ ID NO: 2 and combinations thereof;

a reporter attached to a 5' end of the nucleic acid probe, said reporter capable of emitting a detectable signal;

a quencher attached to a 3' end of the nucleic acid probe capable of substantially quenching the reporter and prevent emission of the detectable signal, when the nucleic acid probe is intact, wherein the reporter becomes substantially unquenched when the nucleic acid probe is cleaved by the polymerase enzyme during amplification of the target nucleic acid sequence;

amplifying the target nucleic acid sequence by thermal cycling, wherein the thermal cycling will amplify the target nucleic acid sequence; and

measuring the level of fluorescence in the sample subsequent to thermal cycling, and further wherein the level of detectable signal is correlated to an amount of the nucleic acid
encoding staphylococcal enterotoxin A in the sample, **thereby quantitatively detecting the nucleic acid encoding staphylococcal enterotoxin A in the sample.**

Letertre et al. teach a method of determining the presence of *staphylococcal* enterotoxin A gene in a sample using Real-Time Fluorogenic Polymerase Chain Reaction (PCR), see title and abstract. Letertre et al. teach the step of contacting a target nucleic acid sequence forming at least a portion of a nucleic acid encoding *staphylococcal* enterotoxin A, with polymerase chain reaction reagents specific for the target nucleic acid sequence, the polymerase chain reaction reagents including forward and reverse primers (see page 140, selection of primers and tables 1-3). Letertre et al. teach a nucleic acid sequence that hybridizes to a portion of the target nucleic acid sequence wherein the portion is unique to the nucleic acid encoding staphylococcal enterotoxin A (see page 140, selection of primers and tables 1-3). Letertre et al. teach a set of universal primers, FastStart Taq DNA polymerase, lighter cycle system from Roche Diagnostics and FastStart DNA Master SYBER Green in a Real –Time fluorescence PCR which covers the limitations (such a reporter attached to a 5' end of the nucleic acid probe, said reporter capable of omitting a detectable signal; and a

quencher attached to a 3' end of the nucleic acid probe capable of substantially quenching the reporter and prevent omission of the detectable signal, when the nucleic acid probe is intact, wherein the reporter becomes substantially unquenched when the nucleic acid probe is cleaved by the polymerase enzyme during amplification of the target nucleic acid sequence), see page 143. Letertre et al. teach amplifying the target nucleic acid sequence by thermal cycling, wherein the thermal cycling is sufficient to amplify the target nucleic acid sequence (see page 142). Letertre et al. also teach measuring the level of fluorescence in the sample subsequent to thermal cycling, and further wherein the level of detectable signal is correlated to an amount of the nucleic acid encoding staphylococcal enterotoxin A in the sample, thereby quantitatively detecting the nucleic acid encoding staphylococcal enterotoxin A in the sample (see page 143). Letertre et al. do not specifically teach sequences such as SEQ ID Nos: 3, 4, 5 or 6. These deficiencies have been overcome by the teaching of Borst et al. (Infection and Immunity vol. 61, no. 12, pp. 5421-5425, 1993 and sequence alignment # STAENAB).

Borst et al. teach primers consisting of sequences from *Staphylococcus aureus* enterotoxin A gene 100% identical to SEQ ID NO: 3, 4 and SEQ ID NO: 5, 6 (see page 5423 and sequence alignment # STAENAB for SEQ ID NO: 3 and NO: 5). Borst et al. also teach primers and probes in the size of 20 to 21 bases in length from an entire sea gene having a length of 1443 bases (see Borst et al. pages 5422-5423 and sequence alignments for SEQ ID # 3, 4 and SEQ ID #5, 6).

Padmapriya et al. teach primers of size of 20 and more nucleotides 100% identical to SEQ ID NO: 1 and 2 which target *Staphylococcus* enterotoxin A gene and used in detecting Staphylococcus aureus causing food poisoning (see abstract, claims and sequence alignment # AED45640).

As to teachings of reporters and quenchers recited in claims 23 and 24 they are already known and commercially available.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the teaching of Letertre et al. ,Borst et al. and Padmapriya et a. to obtain a method of determining the presence of staphylococcal

enterotoxin A gene in a sample because Letertre et al. teach a method of determining the presence of *staphylococcal* enterotoxin A gene in a sample using a Real –Time fluorescence PCR One of ordinary skill in the art would have been motivated to use the sequences taught by Borst et al. as forward and reverse primers because these primers are the nucleic acids from a portion of nucleic acid encoding *staphylococcal* enterotoxin A . Padmapriya et al. teach primers 100% identical to SEQ ID NO: 1 and 2 which target *Staphylococcus* enterotoxin A gene and used in detecting *Staphylococcus aureus*. One would have been motivated to use the already known method and primers of the prior art to detect the presence of *staphylococcal* toxin in a sample.

Applicants' arguments of 9/23/2008 have been considered, but the are not persuasive.

Applicants argue:

- Borst and Padmapriya do not actually teach primers identical to those disclosed and claimed by applicant, and therefore, the combination of Letertre, O'Connell, Borst and Padmapriya does not teach the primers and probes claimed by applicant in the claimed method.

- It is also important to note that while Claim 15 uses the open transitional term "**comprising**" which is open-ended with respect to the overall method steps, it also includes as limitations "a **primer selected from the group consisting** of a forward primer **having a specific sequence** selected from the group consisting of SEQ ID NO: 3, SEQ ID NO: 4 and combinations thereof, and a reverse primer having a specific sequence selected from the group *consisting* of SEQ ID NO: 5, SBQ ID NO: 6 and combinations thereof" and "wherein the nucleic acid sequence of the nucleic acid probe is selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 2." Thus, the specific primers and probes used in applicant's claimed method are specifically limited to the exact sequence listings recited by applicant.

- Applicant readily acknowledges that the general practice of real-time fluorogenic PCR is well established among molecular biologists. However, the assay that is the subject of this patent application is a specific, non-obvious application of the technique designed to detect the presence of nucleic acids encoding the *entA* gene in a sample. The unique, non- obvious feature of the assay is the sequences selected to form the primer and probe oligonucleotides one would use in the performance of the assay. Applicant reiterates that the select/on of specific sequences for PCR primers and probes is not obvious. A researcher should not expect optimal results, or indeed, any results at all, by merely selecting random sequences 20 bases in length to serve as forward and reverse primers. All workers who design PCR assays must obtain several primer pairs and test them empirically to determine which pairs work well (if any at all) under the desired reaction conditions. While Letertre et al. do describe PCR assays that detect the *ent.A* gene, the assays described are up to 25-fold less sensitive than applicant's assays and are clearly not identical.

In response to applicants' arguments applicants attention is brought to the claim language, claim 15 s drawn to a method of determining the presence of staphylococcal enterotoxin A gene in a sample, **comprising:**

contacting a target nucleic acid sequence which **comprises a portion of the *S. aureus ent A* gene encoding staphylococcal enterotoxin A,** with polymerase chain reaction reagents specific for the target nucleic acid sequence, the polymerase chain reaction reagents including a primer selected from the group consisting of a forward primer having a specific sequence selected from the group consisting of SEQ ID NO: 3, SEQ ID NO: 4 and combinations thereof, and a reverse **primer having a specific sequence selected from the group consisting** of SEQ ID NO: 5, SEQ ID NO: 6 and combinations thereof, a polymerase enzyme, and a nucleic acid probe, wherein the nucleic acid probe further **comprises:**

a nucleic acid sequence that hybridizes to a portion of the target nucleic acid sequence **wherein the portion is unique to the nucleic acid encoding staphylococcal enterotoxin A;**

a reporter attached to a 5' end of the nucleic acid probe, said reporter capable of emitting a detectable signal;

a quencher attached to a 3' end of the nucleic acid probe capable of substantially quenching the reporter and prevent emission of the detectable signal, when the nucleic acid probe is intact, wherein the reporter becomes substantially unquenched when the nucleic acid probe is cleaved by the polymerase enzyme during amplification of the target nucleic acid sequence;

amplifying the target nucleic acid sequence by thermal cycling, wherein the thermal cycling will amplify the target nucleic acid sequence; and

measuring the level of fluorescence in the sample subsequent to thermal cycling, and further wherein the level of detectable signal is correlated to an amount of the nucleic acid
encoding staphylococcal enterotoxin A in the sample, **thereby quantitatively detecting the nucleic acid encoding staphylococcal enterotoxin A in the sample.**

The claim language still is an open language having is considered the same as comprising (see **primer having a specific sequence**).

In response to applicants' arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

It is the combination of the prior art the render claim 15 obvious. Letertre et al. teach a method of determining the presence of *staphylococcal* enterotoxin A gene in a sample using Real-Time Fluorogenic Polymerase Chain Reaction (PCR), see title and

abstract. Letertre et al. teach the step of contacting a target nucleic acid sequence forming at least a portion of a nucleic acid encoding *staphylococcal* enterotoxin A, with polymerase chain reaction reagents specific for the target nucleic acid sequence, the polymerase chain reaction reagents including forward and reverse primers (see page 140, selection of primers and tables 1-3). Letertre et al. teach a nucleic acid sequence that hybridizes to a portion of the target nucleic acid sequence wherein the portion is unique to the nucleic acid encoding staphylococcal enterotoxin A (see page 140, selection of primers and tables 1-3). Letertre et al. teach a set of universal primers, FastStart Taq DNA polymerase, lighter cycle system from Roche Diagnostics and FastStart DNA Master SYBER Green in a Real –Time fluorescence PCR which covers the limitations (such a reporter attached to a 5' end of the nucleic acid probe, said reporter capable of omitting a detectable signal; and a quencher attached to a 3' end of the nucleic acid probe capable of substantially quenching the reporter and prevent omission of the detectable signal, when the nucleic acid probe is intact, wherein the reporter becomes substantially unquenched when the nucleic acid probe is cleaved by the polymerase enzyme during amplification of the target nucleic acid sequence), see page 143. Letertre et al. teach amplifying the target nucleic acid sequence by thermal cycling, wherein the thermal cycling is sufficient to amplify the target nucleic acid sequence (see page 142). Letertre et al. also teach measuring the level of fluorescence in the sample subsequent to thermal cycling, and further wherein the level of detectable signal is correlated to an amount of the nucleic acid encoding staphylococcal enterotoxin A in the sample, thereby quantitatively detecting the nucleic acid encoding staphylococcal enterotoxin A in the sample (see page 143).

As to applicants' argument in regard to Borst et al. also teach primers and probes in the size of 20 to 21 bases in length from an entire sea gene having a length of 1443 bases (see Borst et al. pages 5422-5423 and sequence alignments for SEQ ID # 3 and SEQ ID #5) and the same is for Padmapriya.

The examiner agrees with the applicants that that the general practice of real-time fluorogenic PCR is well established among molecular biologists and so is the choice of primers.

Status of Claims

4. No claims are allowed.

Conclusion

5. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Khatol Shahnan-Shah whose telephone number is 571-

272-0863. The examiner can normally be reached on Monday-Friday 7:30 AM-5:00 PM If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi can be reached on 571-272-0956.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Khatol S Shahnan-Shah/
Examiner, Art Unit 1645
January 15 ,2009
/Robert B Mondesi/
Supervisory Patent Examiner, Art Unit 1645